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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/135	A1	(11) International Publication Number: WO 90/06110
		(43) International Publication Date: 14 June 1990 (14.06.90)

(21) International Application Number: PCT/GB89/01383

(22) International Filing Date: 21 November 1989 (21.11.89)

(30) Priority data:
277,240 29 November 1988 (29.11.88) US

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(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, ES (European patent), FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: TREATMENT OF OBESITY

(57) Abstract

N,N-dimethyl-1-1[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride is used in the treatment of obesity in humans.

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Treatment of Obesity

This invention relates to the medical treatment of obesity.

According to the present invention there is provided a method of treating obesity in which a therapeutically effective amount of N,N-dimethyl-1[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride is administered in conjunction with a pharmaceutically acceptable diluent or carrier.

The use of N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of depression is described in British Patent Specification 2098602 and the use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of Parkinson's disease is described in published PCT application WO 88/06444. A particularly preferred form of this compound is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate (sibutramine hydrochloride) which is described in European Patent Application 230742.

The therapeutically active compound may be administered in any of the known pharmaceutical dosage forms for example solid dosage forms such as tablets or capsules or liquid dosage forms for example those forms intended for oral or parenteral administration. The amount of the compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosage of the compound to be administered will be in the range 0.1 to

50 mg preferably 1 to 30 mg per day given in one or more doses.

The ability of sibutramine hydrochloride to cause weight reduction in humans has been demonstrated by the following trials.

Trial 1

39 male healthy volunteer subjects were treated in 3 groups. A first group (Group 1) of 15 subjects were given 2.5 mg sibutramine hydrochloride per day for the first two weeks of the trial, followed by 5 mg sibutramine hydrochloride per day for the remaining four weeks of the trial. The second group (Group 2) of 15 subjects were given 5 mg sibutramine hydrochloride per day for the first two weeks of the trial, followed by 10 mg sibutramine hydrochloride per day for the remaining four weeks of the trial. The third group (Group 3) of 9 subjects were given a placebo containing no sibutramine hydrochloride. The subjects were treated with a single dose of sibutramine hydrochloride or placebo taken each morning of the trial. The weight of each subject was taken at the commencement of treatment and after six weeks. The weight of each subject (in kg) at the start and the change in weight (in kg) over the six week trial period is given in Table 1 below.

TABLE 1

Group 1 given 2.5-5 mg

	weight at start	weight change
	71.4	-3.2
	90.5	-4.1
	74.1	-2.3
	71.4	-2.3
	102.7	-7.2
	74.5	-2.9
	78.2	-4.6
	84.1	0
	63.6	-0.2
	81.4	-2.3
	73.6	-3.6
	87.7	-2.2
	70.0	-4.1
	105.9	+0.5
	85.0	-0.9
mean	80.94 ± 11.99	-2.63 ± 2.01

TABLE 1 (cont)

Group 2 given 5-10 mg

	weight at start	weight change
	76.4	-3.9
5	83.6	-1.8
	73.2	-1.4
	67.3	-2.3
	79.1	0
	78.0	-2.2
10	83.6	-6.3
	76.8	-5.7
	69.5	-1.3
	71.8	-3.6
	82.7	-5.0
15	75.0	-1.4
	75.9	-3.2
	89.8	-3.4
	68.2	-1.8
mean	76.73 ± 6.34	-2.89 ± 1.78

TABLE 1 (cont)

Group 3 given placebo

	weight at start	weight change
	78.1	-1.1
	75.9	-0.4
	77.3	-0.3
	76.4	-1.9
	81.8	-0.7
	60.2	+3.0
	67.3	-2.1
	65.0	-1.8
	73.6	+3.7
mean	72.84 ± 7.09	-0.18 ± 2.11

Trial 2

56 subjects who had been diagnosed as suffering from depression were treated in two groups. A first group (Group 1) of 26 subjects were treated with 10 mg of sibutramine hydrochloride per day for the first two weeks of the trial and then with 20 mg of sibutramine hydrochloride per day for a further period of four weeks. The second group (Group 2) were given a placebo containing no sibutramine hydrochloride every day throughout the trial. The subjects were treated with a single dose of sibutramine hydrochoride or placebo taken each morning of the trial. The weight of each subject was taken at the commencement of the trial and after six weeks. The weight of each subject (in kg) at the start and the change in weight (in kg) over the six week period are given below in Table 2.

TABLE 2

Group 1

	weight at start	weight change
	53.6	-1.1
5	59.5	-1.6
	81.3	+1.4
	84	-3.1
	57.3	-0.3
	78.2	-2.3
10	86.4	-5.0
	78.0	-5.3
	89.8	-0.8
	93.5	-0.6
	64.5	-0.4
15	71.8	-5.0
	81.8	+3.2
	84.5	-2.2
	103.2	-3.2
	55.5	-1.9
20	80.9	-1.4
	67.0	-1.3
	87.2	-4.8
	92.9	0
	96.5	-0.9
25	60.2	-2.2
	68.9	-0.9
	84.7	0.5
	94.7	-1.8
	93.3	-0.7
30 mean	78.4 ± 13.2	-1.6 ± 2.0

TABLE 2 (Cont)

	Group 2	weight at start	weight change
		79.5	+0.5
5		84.4	+1.5
		85.0	-1.6
		89.7	+2.1
		58.2	-5.4
		79.5	-0.9
10		79.5	0
		97.5	+6.1
		66.7	+0.4
		59.5	-0.4
		68.6	+1.9
15		70.9	+0.9
		88.6	+3.2
		89.1	+1.3
		67.7	-0.4
		78.2	-1.8
20		65.5	+0.4
		68.1	+2.1
		74.8	+1.8
		86.4	+0.8
		88.0	-0.6
25		99.2	+1.9
		102.4	+1.3
		68.9	-0.5
		78.8	0
		79.3	+2.2
30		85.6	+0.9
		97.4	-1.6
		46.2	-0.5
		70.2	+0.5
	mean	78.4 ± 13.2	+0.5 ± 2.0

Trial 3

19 male healthy volunteers were treated in 2 groups. A first group (Group 1) of 14 subjects were treated with 15 mg of sibutramine hydrochloride per day for the first two weeks of the trial and then with 30 mg of sibutramine hydrochloride for a further period of four weeks. The second group (Group 2) were given a placebo containing no sibutramine hydrochloride every day throughout the trial. The subjects were treated with a single dose of sibutramine hydrochloride or placebo taken each morning of the trial. The weight of each subject was taken at the commencement of the trial and after six weeks. The weight of each subject (in kg) at the start of the trial and the change in weight (in kg) over the six week period are given below in Table 3.

TABLE 3

Group 1

weight at start	weight change
67.0	-5.4
76.6	-5.5
91.1	-5.5
76.7	-4.7
85.6	-1.3
75.2	-6.8
83.2	-5.5
74.3	-0.9
84.3	-5.9
81.1	0
80.2	-6.8
83.4	-7.0

TABLE 3 (Cont.)

	weight at start	weight change
Group 1		
	77.5	-1.4
	87.4	-4.9
mean	80.3	-4.4 ± 2.4 kg
Group 2		
	84.5	-0.2
	89.7	1.6
	74.3	-0.5
	68.5	2.2
	78.6	0.2
mean	79.1	+0.7 ± 1.2

From the results reported above for Trials 1, 2 and 3 it can be seen that the subjects treated with sibutramine hydrochloride experienced a significant loss of weight over the six week period of each trial when compared to subjects treated with placebo.

Claims

1. A method of treating obesity in humans which comprises administering to a human in need thereof a therapeutically effective amount of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in conjunction with a pharmaceutically acceptable diluent or carrier.

2. A method as claimed in claim 1 wherein N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride is administered in the form of its monohydrate.

3. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine hydrochloride in the manufacture of a medicament for the treatment of obesity.

4. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine hydrochloride monohydrate in the manufacture of a medicament for the treatment of obesity.

5. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of obesity.

6. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine hydrochloride monohydrate in the treatment of obesity.

7. A pharmaceutical composition for the treatment of obesity comprising a therapeutically effective amount of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-

methylbutylamine hydrochloride in conjunction with a pharmaceutically acceptable diluent or carrier.

8. A pharmaceutical composition for the treatment of obesity comprising a therapeutically effective amount of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate in conjunction with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 89/01383

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 31/135

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	WO, A, 88/06444 (THE BOOTS CO. PLC) 7 September 1988, see page 2, lines 5-11 (cited in the application) --	3,4,7,8
Y	Lehrbuch der Pharmakologie und toxikologie, ed. by Hermann Bader, Ed. Medizin Weinheim (DE) page 101, see table B.1.12 --	3,4,7,8
Y	Martindale The Extra Pharmacopoeia, 28th edition, ed. by James E.F. Reynolds The Pharmaceutical Press, 1982 London (GB) page 65, see entry 1470-g	3,4,7,8

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14th February 1990	13. 03. 90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	T.K. WILLIS

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers XX, because they relate to subject matter not required to be searched by this Authority, namely:

xx claims 1,2,5,6

Pls. see Rule 39.1 (iv) - PCT:

Methods for treatment of the human or animal body by surgery and therapy, as well as diagnostic methods.

2. [ ] Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers _____, because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 8901383 SA 32457

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/03/90
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8806444	07-09-88	EP-A- 0282206	14-09-88
		EP-A- 0303677	22-02-89
		JP-T- 1500356	09-02-89
		US-A- 4816488	28-03-89
		US-A- 4871774	03-10-89
		ZA-A- 8801417	02-09-88